REMARKS

Applicants acknowledge receipt of an Office Action dated November 26, 2002.

In the Office Action, the PTO rejected claims 1-18, 23-24, and 28-31 under 35 U.S.C. §112, 2nd paragraph, as allegedly being indefinite and under 35 U.S.C. §112, 1st paragraph as non-enabled by the Specification.

Claims 1-6, 9-18, 23-24 and 28 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent 6,177,401 to Ullrich *et al.* (hereafter "Ullrich") in view of U.S. Patent 5,942,385 to Hirth (hereafter "Hirth"), and further in view of Fingl and Woodbury, The Pharmacological Basis of Therapeutics, Chapter I, pages 25-33 (hereafter "Fingl and Woodbury"). Claims 1-18, 23-24 and 28 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent 5,792,783 to Tang *et al.* (hereafter "Tang") in view of Hirth and further in view of Fingl and Woodbury. Claims 1-18, 23-24 and 28 apparently stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ullrich in view of Hirth, further in view of Tang, and further in view of Fingl and Woodbury. Finally, claims 1-18, 23-24 and 28-31 apparently stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ullrich in view of Tang in further view of Hirth and further in view of Fingl and Woodbury.

In this Response, Applicants have amended claims 1 and 7. Claim 1 has been amended to incorporate the subject matter of claim 22, to delete the phrase, "related to angiogenesis," and to correct a minor typographical error. Claim 7 has been amended to correct for obvious typographical errors. In addition, Applicants have cancelled claim 22 without prejudice or disclaimer. Following entry of these amendments, claims 1-21 and 23-24 and 27-32 are pending in the application.

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the remarks which follow.

Rejections under 35 U.S.C. §112, 1st Paragraph

In the Office Action, the PTO has rejected claims 1-18, 23-24 and 28-31 under 35 U.S.C. §112, 1st paragraph as allegedly being non-enabled.

In this response, Applicants have amended claim 1 to recite the step of "***monitoring a marker selected from the group consisting of tissue factor, CD40, u-PA, ETS-1, IL8, and t-PA***." This amendment deletes the phrase "related to angiogenesis" and inserts the specific markers, "tissue factor, CD40, u-PA, ETS-1, IL8, and t-PA." Applicants submit that the foregoing amendment to claim 1 renders moot the rejection of claims 1-18, 23-24 and 28-31 under 35 U.S.C. §112, 1st paragraph and therefore request reconsideration and withdrawal of this rejection.

Rejections under 35 U.S.C. §112, 2nd Paragraph

In the Office Action, the PTO rejected claims 1-18, 23-24 and 28-31 under 35 U.S.C. §112, 2nd paragraph, as allegedly being indefinite.

In this response, Applicants have deleted the phrase "related to angiogenesis," from step (b) of claim 1 and have corrected a minor typographical error, e.g. substituted the term "steps" for "step". In addition, Applicants have amended claim 7 to correct for obvious typographical errors. Specifically, Applicants have amended line 1 of claim 7 to recite "said compound" which finds antecedent basis in claim 1 and have amended the last line of claim 7 to recite "**or** metabolite thereof."

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the outstanding rejection of claims 1-18, 23-24 and 28-31 under 35 U.S.C. §112, 2nd paragraph.

Rejections Under 35 U.S.C. §103

In the Office Action, the PTO rejected claims 1-18, 23-24 and 28-31 under 35 U.S.C. §103(a) as allegedly being unpatentable over various combinations of Ullrich, Tang, Hirth and Fingl and Woodbury.

In this response, Applicants have amended claim 1 to recite the step of "***monitoring a marker selected from the group consisting of tissue factor, CD40, u-PA, ETS-1, IL8, and t-PA***."

In order to establish *prima facie* obviousness of a claimed invention, all the limitations must be taught or suggested by the prior art. *In re Royka*, 180 USPQ 580 (CCPA 1974). See generally MPEP §2143.03.

Here, none of Ullrich, Tang, Hirth and Fingl and Woodbury, taken individually or in any fair combination, teach or suggest the step of ***monitoring a marker selected from the group consisting of tissue factor, CD40, u-PA, ETS-1, IL8, and t-PA*** as recited in amended claim 1. For this reason, Applicants submit that the foregoing amendments and remarks render moot the outstanding rejections of claims 1-18, 23-24 and 28-31 under 35 U.S.C. §103(a) and respectfully request reconsideration and withdrawal of these rejections.

CONCLUSION

In view of the foregoing amendments and remarks, applicants respectfully submit that all of the pending claims are now in condition for allowance. An early notice to this effect is earnestly solicited. If there are any questions regarding the application, the Examiner is invited to contact the undersigned at the number below.

Respectfully submitted,

Date 2/26/02

By [signature] for Reg. No. 47,369

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Versions with Markings to Show Changes Made

In the Claims:

Claim 1. (Amended) A method of determining an efficacious dose of a compound administered to a subject for the purpose of modulating angiogenesis, comprising the **[step]** steps of

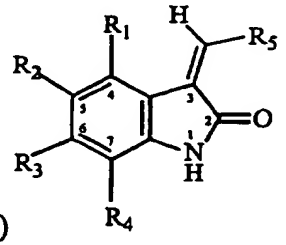
(a) administering the compound to a patient;

(b) monitoring a marker **[related to angiogenesis]** **selected from the group consisting of tissue factor, CD40, u-PA, ETS-1, IL8, and t-PA**;

(c) constructing a standard curve; and

(d) determining the efficacious dose based on the standard curve.

Claim 7. (Amended) The method of claim 5, wherein **[said drug]** **said compound** is an indolinone compound, having the structure set forth in formula I:



(I)

wherein

(a) R1, R2, R3, and R4 are selected from the group consisting of hydrogen, trihalomethyl, hydroxyl, amine, thioether, cyano, alkoxy, alkyl, amino, bromo, fluoro, chloro, iodo, mercapto, thio, cyanoamido, alkylthio, aryl, heteroaryl, carboxyl, ester, oxo, alkoxycarbonyl, alkenyl, alkoxy, nitro, alkoxyl, and amido moieties; and

(b) R5, is an optionally substituted aryl or heteroaryl cyclic moiety;

or a pharmaceutically acceptable salt, ester, amide, prodrug, isomer, **[and]** **or** metabolite thereof.